

FIG. 1.

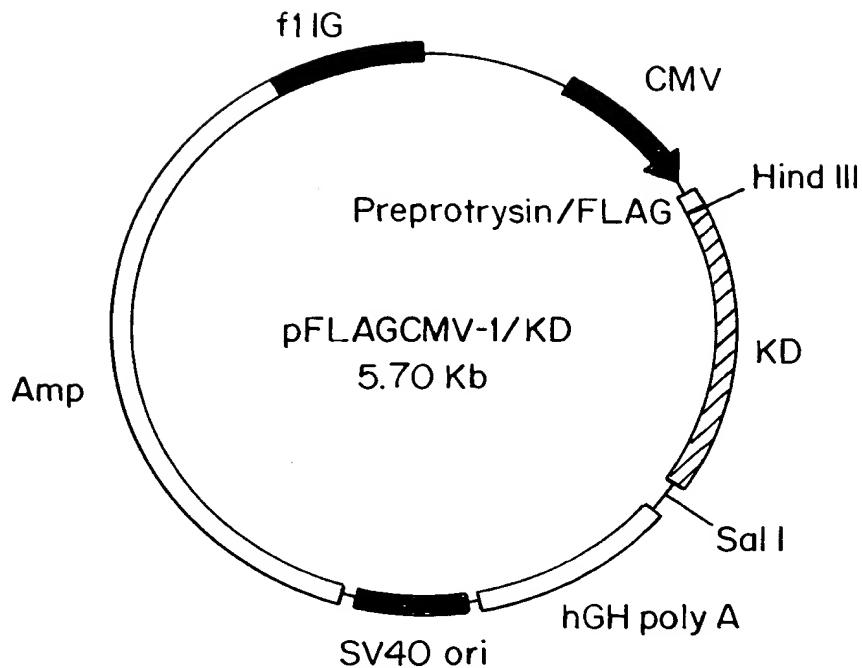


FIG. 2.

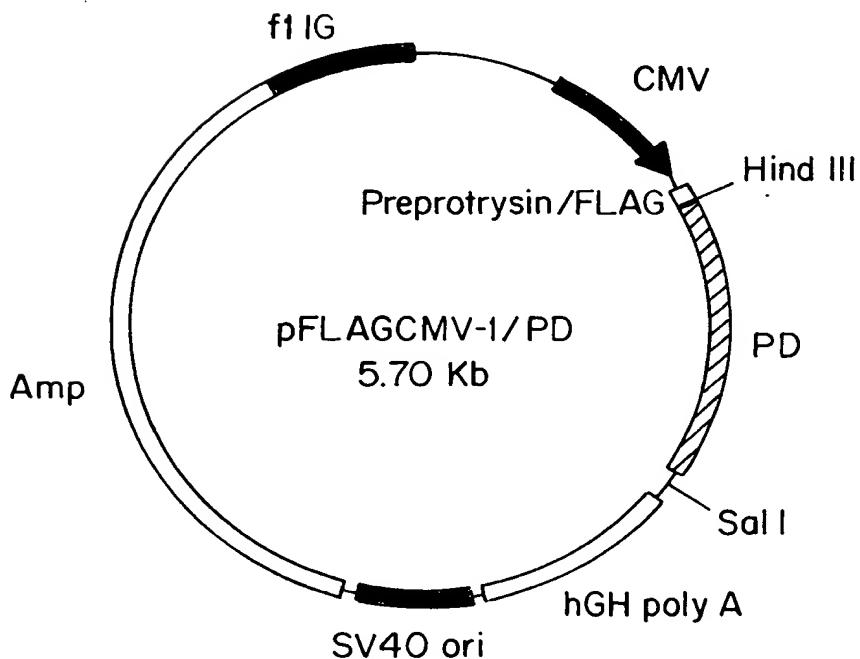


FIG. 3.

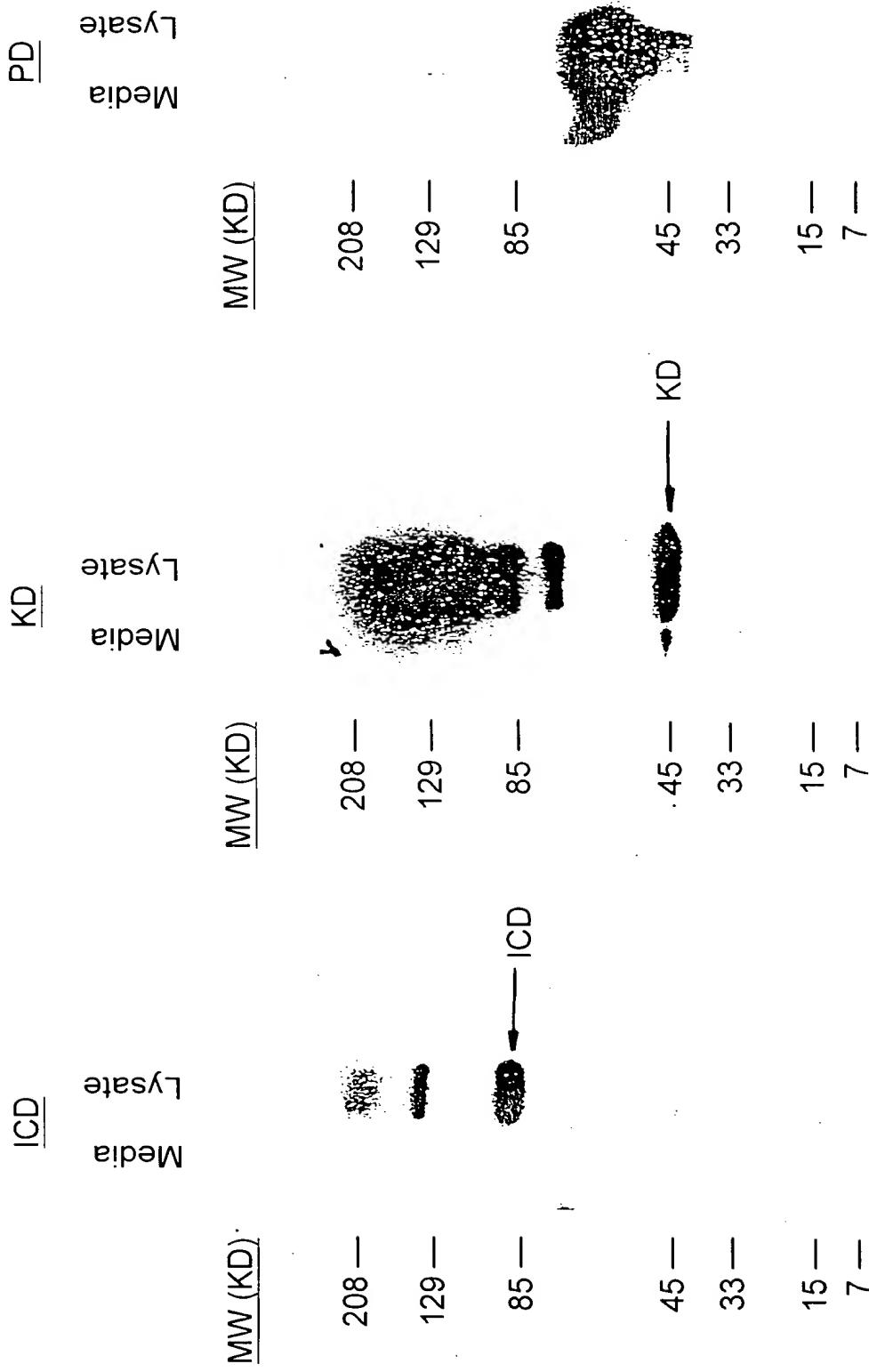


FIG. 4.

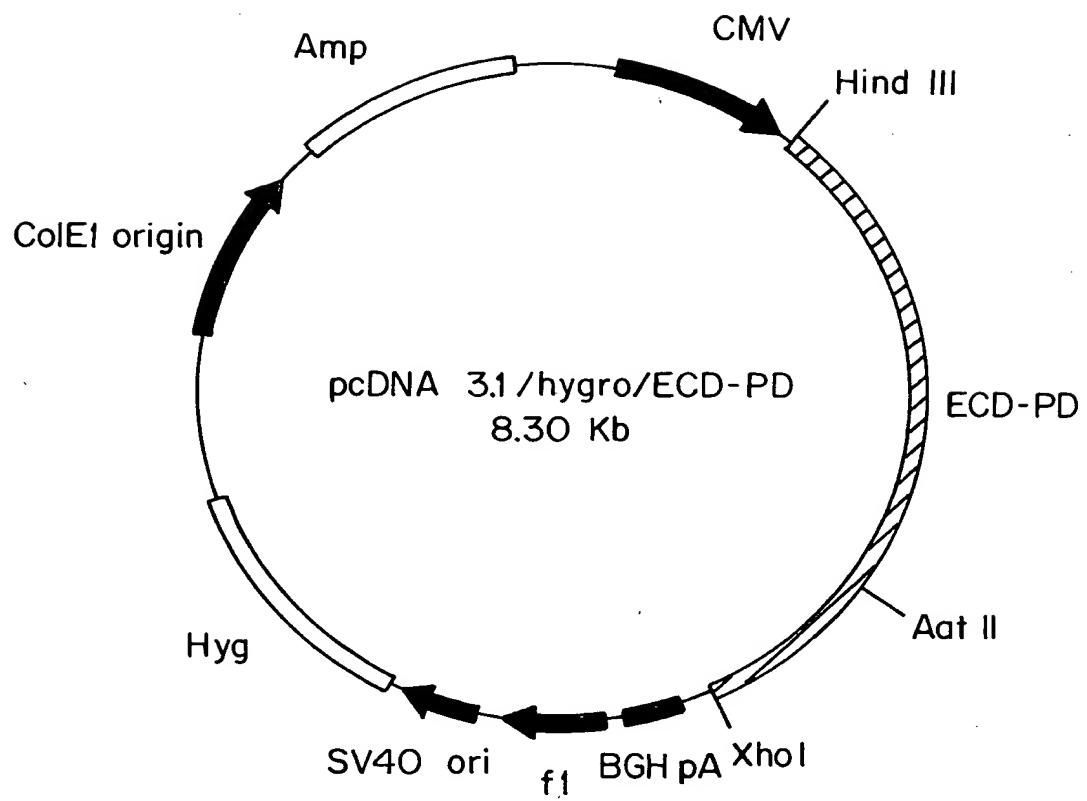


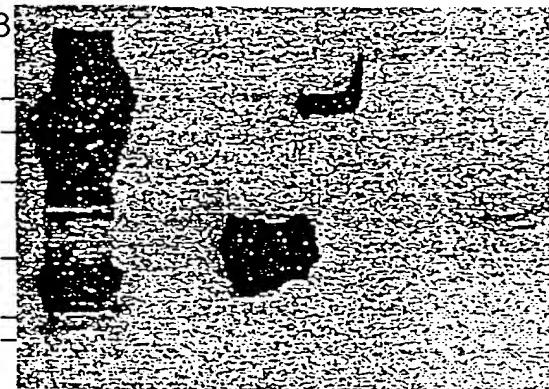
FIG. 5.

pcDNA3.1hyg/ECD-PD expression

FIG. 6A.

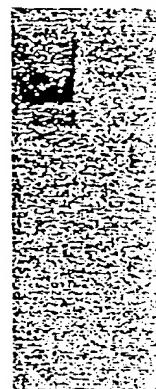
293T

Her2/neu AB-3

203
116
83
49
37
28

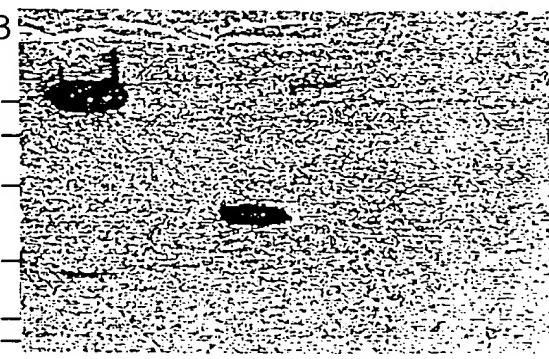
pcDNA3.1hyg/ECD-PD
media
lysate

anti ECD

**FIG. 6B.**

CHO

Her2/neu AB-3

203
116
83
49
37
28

09854356 020402

6/47

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
1 5 10 15

Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
20 25 30

Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
50 55 60

Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
65 70 75 80

Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
85 90 95

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
100 105 110

Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
115 120 125

Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser
130 135 140

Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
145 150 155 160

Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
165 170 175

Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
180 185 190

His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
195 200 205

Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
210 215 220

Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
225 230 235 240

Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
245 250 255

FIG. 7. (SEQ ID NO: 1)

7/47

His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
260 265 270

Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
275 280 285

Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
290 295 300

Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
305 310 315 320

Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
325 330 335

Pro Cys Ala Arg Val Cys Tyr Gly Leu Gly Met Glu His Leu Arg Glu
340 345 350

Val Arg Ala Val Thr Ser Ala Asn Ile Gln Glu Phe Ala Gly Cys Lys
355 360 365

Lys Ile Phe Gly Ser Leu Ala Phe Leu Pro Glu Ser Phe Asp Gly Asp
370 375 380

Pro Ala Ser Asn Thr Ala Pro Leu Gln Pro Glu Gln Leu Gln Val Phe
385 390 395 400

Glu Thr Leu Glu Glu Ile Thr Gly Tyr Leu Tyr Ile Ser Ala Trp Pro
405 410 415

Asp Ser Leu Pro Asp Leu Ser Val Phe Gln Asn Leu Gln Val Ile Arg
420 425 430

Gly Arg Ile Leu His Asn Gly Ala Tyr Ser Leu Thr Leu Gln Gly Leu
435 440 445

Gly Ile Ser Trp Leu Gly Leu Arg Ser Leu Arg Glu Leu Gly Ser Gly
450 455 460

Leu Ala Leu Ile His His Asn Thr His Leu Cys Phe Val His Thr Val
465 470 475 480

Pro Trp Asp Gln Leu Phe Arg Asn Pro His Gln Ala Leu Leu His Thr
485 490 495

Ala Asn Arg Pro Glu Asp Glu Cys Val Gly Glu Gly Leu Ala Cys His
500 505 510

FIG. 7. (CONTINUED)

8/47

Gln Leu Cys Ala Arg Gly His Cys Trp Gly Pro Gly Pro Thr Gln Cys
515 520 525

Val Asn Cys Ser Gln Phe Leu Arg Gly Gln Glu Cys Val Glu Glu Cys
530 535 540

Arg Val Leu Gln Gly Leu Pro Arg Glu Tyr Val Asn Ala Arg His Cys
545 550 555 560

Leu Pro Cys His Pro Glu Cys Gln Pro Gln Asn Gly Ser Val Thr Cys
565 570 575

Phe Gly Pro Glu Ala Asp Gln Cys Val Ala Cys Ala His Tyr Lys Asp
580 585 590

Pro Pro Phe Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro Asp Leu
595 600 605

Ser Tyr Met Pro Ile Trp Lys Phe Pro Asp Glu Glu Gly Ala Cys Gln
610 615 620

Pro Cys Pro Ile Asn Cys Thr His Ser Cys Val Asp Leu Asp Asp Lys
625 630 635 640

Gly Cys Pro Ala Glu Gln Arg Ala Ser Pro Leu Thr Ser Ile Ile Ser
645 650 655

Ala Val Val Gly Ile Leu Leu Val Val Val Leu Gly Val Val Phe Gly
660 665 670

Ile Leu Ile Lys Arg Arg Gln Gln Lys Ile Arg Lys Tyr Thr Met Arg
675 680 685

Arg Leu Leu Gln Glu Thr Glu Leu Val Glu Pro Leu Thr Pro Ser Gly
690 695 700

Ala Met Pro Asn Gln Ala Gln Met Arg Ile Leu Lys Glu Thr Glu Leu
705 710 715 720

Arg Lys Val Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr Lys
725 730 735

Gly Ile Trp Ile Pro Asp Gly Glu Asn Val Lys Ile Pro Val Ala Ile
740 745 750

Lys Val Leu Arg Glu Asn Thr Ser Pro Lys Ala Asn Lys Glu Ile Leu
755 760 765

FIG. 7. (CONTINUED)

9/47

Asp Glu Ala Tyr Val Met Ala Gly Val Gly Ser Pro Tyr Val Ser Arg
770 775 780

Leu Leu Gly Ile Cys Leu Thr Ser Thr Val Gln Leu Val Thr Gln Leu
785 790 795 800

Met Pro Tyr Gly Cys Leu Leu Asp His Val Arg Glu Asn Arg Gly Arg
805 810 815

Leu Gly Ser Gln Asp Leu Leu Asn Trp Cys Met Gln Ile Ala Lys Gly
820 825 830

Met Ser Tyr Leu Glu Asp Val Arg Leu Val His Arg Asp Leu Ala Ala
835 840 845

Arg Asn Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr Asp Phe
850 855 860

Gly Leu Ala Arg Leu Leu Asp Ile Asp Glu Thr Glu Tyr His Ala Asp
865 870 875 880

Gly Gly Lys Val Pro Ile Lys Trp Met Ala Leu Glu Ser Ile Leu Arg
885 890 895

Arg Arg Phe Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Val
900 905 910

Trp Glu Leu Met Thr Phe Gly Ala Lys Pro Tyr Asp Gly Ile Pro Ala
915 920 925

Arg Glu Ile Pro Asp Leu Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro
930 935 940

Pro Ile Cys Thr Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp Met
945 950 955 960

Ile Asp Ser Glu Cys Arg Pro Arg Phe Arg Glu Leu Val Ser Glu Phe
965 970 975

Ser Arg Met Ala Arg Asp Pro Gln Arg Phe Val Val Ile Gln Asn Glu
980 985 990

Asp Leu Gly Pro Ala Ser Pro Leu Asp Ser Thr Phe Tyr Arg Ser Leu
995 1000 1005

Leu Glu Asp Asp Asp Met Gly Asp Leu Val Asp Ala Glu Glu Tyr Leu
1010 1015 1020

FIG. 7. (CONTINUED)

10/47

Val Pro Gln Gln Gly Phe Phe Cys Pro Asp Pro Ala Pro Gly Ala Gly
1025 1030 1035 1040

Gly Met Val His His Arg His Arg Ser Ser Ser Thr Arg Ser Gly Gly
1045 1050 1055

Gly Asp Leu Thr Leu Gly Leu Glu Pro Ser Glu Glu Glu Ala Pro Arg
1060 1065 1070

Ser Pro Leu Ala Pro Ser Glu Gly Ala Gly Ser Asp Val Phe Asp Gly
1075 1080 1085

Asp Leu Gly Met Gly Ala Ala Lys Gly Leu Gln Ser Leu Pro Thr His
1090 1095 1100

Asp Pro Ser Pro Leu Gln Arg Tyr Ser Glu Asp Pro Thr Val Pro Leu
1105 1110 1115 1120

Pro Ser Glu Thr Asp Gly Tyr Val Ala Pro Leu Thr Cys Ser Pro Gln
1125 1130 1135

Pro Glu Tyr Val Asn Gln Pro Asp Val Arg Pro Gln Pro Pro Ser Pro
1140 1145 1150

Arg Glu Gly Pro Leu Pro Ala Ala Arg Pro Ala Gly Ala Thr Leu Glu
1155 1160 1165

Arg Pro Lys Thr Leu Ser Pro Gly Lys Asn Gly Val Val Lys Asp Val
1170 1175 1180

Phe Ala Phe Gly Gly Ala Val Glu Asn Pro Glu Tyr Leu Thr Pro Gln
1185 1190 1195 1200

Gly Gly Ala Ala Pro Gln Pro His Pro Pro Pro Ala Phe Ser Pro Ala
1205 1210 1215

Phe Asp Asn Leu Tyr Tyr Trp Asp Gln Asp Pro Pro Glu Arg Gly Ala
1220 1225 1230

Pro Pro Ser Thr Phe Lys Gly Thr Pro Thr Ala Glu Asn Pro Glu Tyr
1235 1240 1245

Leu Gly Leu Asp Val Pro Val * *
1250 1255 1257

FIG. 7. (CONTINUED)

11/47

Met Glu Leu Ala Ala Trp Cys Arg Trp Gly Phe Leu Leu Ala Leu Leu
1 5 10 15

Pro Pro Gly Ile Ala Gly Thr Gln Val Cys Thr Gly Thr Asp Met Lys
20 25 30

Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
50 55 60

Val Pro Ala Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
65 70 75 80

Gln Gly Tyr Met Leu Ile Ala His Asn Gln Val Lys Arg Val Pro Leu
85 90 95

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Lys Tyr
100 105 110

Ala Leu Ala Val Leu Asp Asn Arg Asp Pro Gln Asp Asn Val Ala Ala
115 120 125

Ser Thr Pro Gly Arg Thr Pro Glu Gly Leu Arg Glu Leu Gln Leu Arg
130 135 140

Ser Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Arg Gly Asn Pro
145 150 155 160

Gln Leu Cys Tyr Gln Asp Met Val Leu Trp Lys Asp Val Phe Arg Lys
165 170 175

Asn Asn Gln Leu Ala Pro Val Asp Ile Asp Thr Asn Arg Ser Arg Ala
180 185 190

Cys Pro Pro Cys Ala Pro Ala Cys Lys Asp Asn His Cys Trp Gly Glu
195 200 205

Ser Pro Glu Asp Cys Gln Ile Leu Thr Gly Thr Ile Cys Thr Ser Gly
210 215 220

Cys Ala Arg Cys Lys Gly Arg Leu Pro Thr Asp Cys Cys His Glu Gln
225 230 235 240

Cys Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys
245 250 255

FIG. 8. (SEQ ID NO:2)

12/47

Leu His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu
260 265 270

Val Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met His Asn Pro Glu Gly
275 280 285

Arg Tyr Thr Phe Gly Ala Ser Cys Val Thr Thr Cys Pro Tyr Asn Tyr
290 295 300

Leu Ser Thr Glu Val Gly Ser Cys Thr Leu Val Cys Pro Pro Asn Asn
305 310 315 320

Gln Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser
325 330 335

Lys Pro Cys Ala Arg Val Cys Tyr Gly Leu Gly Met Glu His Leu Arg
340 345 350

Gly Ala Arg Ala Ile Thr Ser Asp Asn Val Gln Glu Phe Asp Gly Cys
355 360 365

Lys Lys Ile Phe Gly Ser Leu Ala Phe Leu Pro Glu Ser Phe Asp Gly
370 375 380

Asp Pro Ser Ser Gly Ile Ala Pro Leu Arg Pro Glu Gln Leu Gln Val
385 390 395 400

Phe Glu Thr Leu Glu Glu Ile Thr Gly Tyr Leu Tyr Ile Ser Ala Trp
405 410 415

Pro Asp Ser Leu Arg Asp Leu Ser Val Phe Gln Asn Leu Arg Ile Ile
420 425 430

Arg Gly Arg Ile Leu His Asp Gly Ala Tyr Ser Leu Thr Leu Gln Gly
435 440 445

Leu Gly Ile His Ser Leu Gly Leu Arg Ser Leu Arg Glu Leu Gly Ser
450 455 460

Gly Leu Ala Leu Ile His Arg Asn Ala His Leu Cys Phe Val His Thr
465 470 475 480

Val Pro Trp Asp Gln Leu Phe Arg Asn Pro His Gln Ala Leu Leu His
485 490 495

Ser Gly Asn Arg Pro Glu Glu Asp Cys Gly Leu Glu Gly Leu Val Cys
500 505 510

FIG. 8. (CONTINUED)

13/47

Asn Ser Leu Cys Ala His Gly His Cys Trp Gly Pro Gly Pro Thr Gln
515 520 525

Cys Val Asn Cys Ser His Phe Leu Arg Gly Gln Glu Cys Val Glu Glu
530 535 540

Cys Arg Val Trp Lys Gly Leu Pro Arg Glu Tyr Val Ser Asp Lys Arg
545 550 555 560

Cys Leu Pro Cys His Pro Glu Cys Gln Pro Gln Asn Ser Ser Glu Thr
565 570 575

Cys Phe Gly Ser Glu Ala Asp Gln Cys Ala Ala Cys Ala His Tyr Lys
580 585 590

Asp Ser Ser Ser Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro Asp
595 600 605

Leu Ser Tyr Met Pro Ile Trp Lys Tyr Pro Asp Glu Glu Gly Ile Cys
610 615 620

Gln Pro Cys Pro Ile Asn Cys Thr His Ser Cys Val Asp Leu Asp Glu
625 630 635 640

Arg Gly Cys Pro Ala Glu Gln Arg Ala Ser Pro Val Thr Phe Ile Ile
645 650 655

Ala Thr Val Glu Gly Val Leu Leu Phe Leu Ile Leu Val Val Val Val
660 665 670

Gly Ile Leu Ile Lys Arg Arg Arg Gln Lys Ile Arg Lys Tyr Thr Met
675 680 685

Arg Arg Leu Leu Gln Glu Thr Glu Leu Val Glu Pro Leu Thr Pro Ser
690 695 700

Gly Ala Met Pro Asn Gln Ala Gln Met Arg Ile Leu Lys Glu Thr Glu
705 710 715 720

Leu Arg Lys Val Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr
725 730 735

Lys Gly Ile Trp Ile Pro Asp Gly Glu Asn Val Lys Ile Pro Val Ala
740 745 750

Ile Lys Val Leu Arg Glu Asn Thr Ser Pro Lys Ala Asn Lys Glu Ile
755 760 765

FIG. 8. (CONTINUED)

14/47

Leu Asp Glu Ala Tyr Val Met Ala Gly Val Gly Ser Pro Tyr Val Ser
770 775 780

Arg Leu Leu Gly Ile Cys Leu Thr Ser Thr Val Gln Leu Val Thr Gln
785 790 795 800

Leu Met Pro Tyr Gly Cys Leu Leu Asp His Val Arg Glu His Arg Gly
805 810 815

Arg Leu Gly Ser Gln Asp Leu Leu Asn Trp Cys Val Gln Ile Ala Lys
820 825 830

Gly Met Ser Tyr Leu Glu Asp Val Arg Leu Val His Arg Asp Leu Ala
835 840 845

Ala Arg Asn Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr Asp
850 855 860

Phe Gly Leu Ala Arg Leu Leu Asp Ile Asp Glu Thr Glu Tyr His Ala
865 870 875 880

Asp Gly Gly Lys Val Pro Ile Lys Trp Met Ala Leu Glu Ser Ile Leu
885 890 895

Arg Arg Arg Phe Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr
900 905 910

Val Trp Glu Leu Met Thr Phe Gly Ala Lys Pro Tyr Asp Gly Ile Pro
915 920 925

Ala Arg Glu Ile Pro Asp Leu Leu Glu Lys Gly Glu Arg Leu Pro Gln
930 935 940

Pro Pro Ile Cys Thr Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp
945 950 955 960

Met Ile Asp Ser Glu Cys Arg Pro Arg Phe Arg Glu Leu Val Ser Glu
965 970 975

Phe Ser Arg Met Ala Arg Asp Pro Gln Arg Phe Val Val Ile Gln Asn
980 985 990

Glu Asp Leu Gly Pro Ser Ser Pro Met Asp Ser Thr Phe Tyr Arg Ser
995 1000 1005

Leu Leu Glu Asp Asp Asp Met Gly Asp Leu Val Asp Ala Glu Glu Tyr
1010 1015 1020

FIG. 8. (CONTINUED)

15/47

Leu Val Pro Gln Gln Gly Phe Phe Ser Pro Asp Pro Thr Pro Gly Thr
1025 1030 1035 1040

Gly Ser Thr Ala His Arg Arg His Arg Ser Ser Ser Thr Arg Ser Gly
1045 1050 1055

Gly Gly Glu Leu Thr Leu Gly Leu Glu Pro Ser Glu Glu Gly Pro Pro
1060 1065 1070

Arg Ser Pro Leu Ala Pro Ser Glu Gly Ala Gly Ser Asp Val Phe Asp
1075 1080 1085

Gly Asp Leu Ala Met Gly Val Thr Lys Gly Leu Gln Ser Leu Ser Pro
1090 1095 1100

His Asp Leu Ser Pro Leu Gln Arg Tyr Ser Glu Asp Pro Thr Leu Pro
1105 1110 1115 1120

Leu Pro Pro Glu Thr Asp Gly Tyr Val Ala Pro Leu Ala Cys Ser Pro
1125 1130 1135

Gln Pro Glu Tyr Val Asn Gln Ser Glu Val Gln Pro Gln Pro Pro Leu
1140 1145 1150

Thr Pro Glu Gly Pro Leu Pro Pro Val Arg Pro Ala Gly Ala Thr Leu
1155 1160 1165

Glu Arg Pro Lys Thr Leu Ser Pro Gly Lys Asn Gly Val Val Lys Asp
1170 1175 1180

Val Phe Ala Phe Gly Gly Ala Val Glu Asn Pro Glu Tyr Leu Val Pro
1185 1190 1195 1200

Arg Glu Gly Thr Ala Ser Pro Pro His Pro Ser Pro Ala Phe Ser Pro
1205 1210 1215

Ala Phe Asp Asn Leu Tyr Tyr Trp Asp Gln Asn Ser Ser Glu Gln Gly
1220 1225 1230

Pro Pro Pro Ser Asn Phe Glu Gly Thr Pro Thr Ala Glu Asn Pro Glu
1235 1240 1245

Tyr Leu Gly Leu Asp Val Pro Val * *
1250 1255 1258

FIG. 8. (CONTINUED)

16/47

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
1 5 10 15

Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
20 25 30

Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
50 55 60

Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
65 70 75 80

Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
85 90 95

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
100 105 110

Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
115 120 125

Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser
130 135 140

Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
145 150 155 160

Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
165 170 175

Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
180 185 190

His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
195 200 205

Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
210 215 220

Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
225 230 235 240

Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
245 250 255

FIG. 9. (SEQ ID NO: 3)

17/47

His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
260 265 270

Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
275 280 285

Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
290 295 300

Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
305 310 315 320

Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
325 330 335

Pro Cys Ala Arg Val Cys Tyr Gly Leu Gly Met Glu His Leu Arg Glu
340 345 350

Val Arg Ala Val Thr Ser Ala Asn Ile Gln Glu Phe Ala Gly Cys Lys
355 360 365

Lys Ile Phe Gly Ser Leu Ala Phe Leu Pro Glu Ser Phe Asp Gly Asp
370 375 380

Pro Ala Ser Asn Thr Ala Pro Leu Gln Pro Glu Gln Leu Gln Val Phe
385 390 395 400

Glu Thr Leu Glu Glu Ile Thr Gly Tyr Leu Tyr Ile Ser Ala Trp Pro
405 410 415

Asp Ser Leu Pro Asp Leu Ser Val Phe Gln Asn Leu Gln Val Ile Arg
420 425 430

Gly Arg Ile Leu His Asn Gly Ala Tyr Ser Leu Thr Leu Gln Gly Leu
435 440 445

Gly Ile Ser Trp Leu Gly Leu Arg Ser Leu Arg Glu Leu Gly Ser Gly
450 455 460

Leu Ala Leu Ile His His Asn Thr His Leu Cys Phe Val His Thr Val
465 470 475 480

Pro Trp Asp Gln Leu Phe Arg Asn Pro His Gln Ala Leu Leu His Thr
485 490 495

Ala Asn Arg Pro Glu Asp Glu Cys Val Gly Glu Gly Leu Ala Cys His
500 505 510

FIG. 9. (CONTINUED)

18/47

Gln Leu Cys Ala Arg Gly His Cys Trp Gly Pro Gly Pro Thr Gln Cys
515 520 525

Val Asn Cys Ser Gln Phe Leu Arg Gly Gln Glu Cys Val Glu Glu Cys
530 535 540

Arg Val Leu Gln Gly Leu Pro Arg Glu Tyr Val Asn Ala Arg His Cys
545 550 555 560

Leu Pro Cys His Pro Glu Cys Gln Pro Gln Asn Gly Ser Val Thr Cys
565 570 575

Phe Gly Pro Glu Ala Asp Gln Cys Val Ala Cys Ala His Tyr Lys Asp
580 585 590

Pro Pro Phe Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro Asp Leu
595 600 605

Ser Tyr Met Pro Ile Trp Lys Phe Pro Asp Glu Glu Gly Ala Cys Gln
610 615 620

Pro Cys Pro Ile Asn Cys Thr His Ser Cys Val Asp Leu Asp Asp Lys
625 630 635 640

Gly Cys Pro Ala Glu Gln Arg Ala Ser Pro Leu Thr Ser
645 650 653

FIG. 9. (CONTINUED)

Gln Asn Glu Asp Leu Gly Pro Ala Ser Pro Leu Asp Ser Thr Phe Tyr
1 5 10 15

Arg Ser Leu Leu Glu Asp Asp Asp Met Gly Asp Leu Val Asp Ala Glu
20 25 30

Glu Tyr Leu Val Pro Gln Gln Gly Phe Phe Cys Pro Asp Pro Ala Pro
35 40 45

Gly Ala Gly Gly Met Val His His Arg His Arg Ser Ser Ser Thr Arg
50 55 60

Ser Gly Gly Gly Asp Leu Thr Leu Gly Leu Glu Pro Ser Glu Glu Glu
65 70 75 80

Ala Pro Arg Ser Pro Leu Ala Pro Ser Glu Gly Ala Gly Ser Asp Val
85 90 95

FIG. 10. (SEQ ID NO: 4)

19/47

Phe Asp Gly Asp Leu Gly Met Gly Ala Ala Lys Gly Leu Gln Ser Leu
100 105 110

Pro Thr His Asp Pro Ser Pro Leu Gln Arg Tyr Ser Glu Asp Pro Thr
115 120 125

Val Pro Leu Pro Ser Glu Thr Asp Gly Tyr Val Ala Pro Leu Thr Cys
130 135 140

Ser Pro Gln Pro Glu Tyr Val Asn Gln Pro Asp Val Arg Pro Gln Pro
145 150 155 160

Pro Ser Pro Arg Glu Gly Pro Leu Pro Ala Ala Arg Pro Ala Gly Ala
165 170 175

Thr Leu Glu Arg Pro Lys Thr Leu Ser Pro Gly Lys Asn Gly Val Val
180 185 190

Lys Asp Val Phe Ala Phe Gly Gly Ala Val Glu Asn Pro Glu Tyr Leu
195 200 205

Thr Pro Gln Gly Gly Ala Ala Pro Gln Pro His Pro Pro Pro Ala Phe
210 215 220

Ser Pro Ala Phe Asp Asn Leu Tyr Tyr Trp Asp Gln Asp Pro Pro Glu
225 230 235 240

Arg Gly Ala Pro Pro Ser Thr Phe Lys Gly Thr Pro Thr Ala Glu Asn
245 250 255

Pro Glu Tyr Leu Gly Leu Asp Val Pro Val *
260 265 267

FIG. 10. (CONTINUED)

Gln Asn Glu Asp Leu Gly Pro Ala Ser Pro Leu Asp Ser Thr Phe Tyr
1 5 10 15

Arg Ser Leu Leu Glu Asp Asp Asp Met Gly Asp Leu Val Asp Ala Glu
20 25 30

Glu Tyr Leu Val Pro Gln Gln Gly Phe Phe Cys Pro Asp Pro Ala Pro
35 40 45

Gly Ala Gly Gly Met Val His His Arg His Arg *
50 55 60

FIG. 11. (SEQ ID NO: 5)

20/47

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
1 5 10 15

Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
20 25 30

Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
50 55 60

Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
65 70 75 80

Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
85 90 95

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
100 105 110

Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
115 120 125

Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser
130 135 140

Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
145 150 155 160

Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
165 170 175

Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
180 185 190

His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
195 200 205

Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
210 215 220

Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
225 230 235 240

Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
245 250 255

FIG. 12. (SEQ ID NO: 6)

21/47

His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
260 265 270

Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
275 280 285

Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
290 295 300

Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
305 310 315 320

Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
325 330 335

Pro Cys Ala Arg Val Cys Tyr Gly Leu Gly Met Glu His Leu Arg Glu
340 345 350

Val Arg Ala Val Thr Ser Ala Asn Ile Gln Glu Phe Ala Gly Cys Lys
355 360 365

Lys Ile Phe Gly Ser Leu Ala Phe Leu Pro Glu Ser Phe Asp Gly Asp
370 375 380

Pro Ala Ser Asn Thr Ala Pro Leu Gln Pro Glu Gln Leu Gln Val Phe
385 390 395 400

Glu Thr Leu Glu Glu Ile Thr Gly Tyr Leu Tyr Ile Ser Ala Trp Pro
405 410 415

Asp Ser Leu Pro Asp Leu Ser Val Phe Gln Asn Leu Gln Val Ile Arg
420 425 430

Gly Arg Ile Leu His Asn Gly Ala Tyr Ser Leu Thr Leu Gln Gly Leu
435 440 445

Gly Ile Ser Trp Leu Gly Leu Arg Ser Leu Arg Glu Leu Gly Ser Gly
450 455 460

Leu Ala Leu Ile His His Asn Thr His Leu Cys Phe Val His Thr Val
465 470 475 480

Pro Trp Asp Gln Leu Phe Arg Asn Pro His Gln Ala Leu Leu His Thr
485 490 495

Ala Asn Arg Pro Glu Asp Glu Cys Val Gly Glu Gly Leu Ala Cys His
500 505 510

FIG. 12. (CONTINUED)

22/47

Gln Leu Cys Ala Arg Gly His Cys Trp Gly Pro Gly Pro Thr Gln Cys
515 520 525

Val Asn Cys Ser Gln Phe Leu Arg Gly Gln Glu Cys Val Glu Glu Cys
530 535 540

Arg Val Leu Gln Gly Leu Pro Arg Glu Tyr Val Asn Ala Arg His Cys
545 550 555 560

Leu Pro Cys His Pro Glu Cys Gln Pro Gln Asn Gly Ser Val Thr Cys
565 570 575

Phe Gly Pro Glu Ala Asp Gln Cys Val Ala Cys Ala His Tyr Lys Asp
580 585 590

Pro Pro Phe Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro Asp Leu
595 600 605

Ser Tyr Met Pro Ile Trp Lys Phe Pro Asp Glu Glu Gly Ala Cys Gln
610 615 620

Pro Cys Pro Ile Asn Cys Thr His Ser Cys Val Asp Leu Asp Asp Lys
625 630 635 640

Gly Cys Pro Ala Glu Gln Arg Ala Ser Pro Leu Thr Ser Gln Asn Glu
645 650 655

Asp Leu Gly Pro Ala Ser Pro Leu Asp Ser Thr Phe Tyr Arg Ser Leu
660 665 670

Leu Glu Asp Asp Asp Met Gly Asp Leu Val Asp Ala Glu Glu Tyr Leu
675 680 685

Val Pro Gln Gln Gly Phe Phe Cys Pro Asp Pro Ala Pro Gly Ala Gly
690 695 700

Gly Met Val His His Arg His Arg Ser Ser Ser Thr Arg Ser Gly Gly
705 710 715 720

Gly Asp Leu Thr Leu Gly Leu Glu Pro Ser Glu Glu Glu Ala Pro Arg
725 730 735

Ser Pro Leu Ala Pro Ser Glu Gly Ala Gly Ser Asp Val Phe Asp Gly
740 745 750

Asp Leu Gly Met Gly Ala Ala Lys Gly Leu Gln Ser Leu Pro Thr His
755 760 765

FIG. 12. (CONTINUED)

23/47

Asp Pro Ser Pro Leu Gln Arg Tyr Ser Glu Asp Pro Thr Val Pro Leu
770 775 780

Pro Ser Glu Thr Asp Gly Tyr Val Ala Pro Leu Thr Cys Ser Pro Gln
785 790 795 800

Pro Glu Tyr Val Asn Gln Pro Asp Val Arg Pro Gln Pro Pro Ser Pro
805 810 815

Arg Glu Gly Pro Leu Pro Ala Ala Arg Pro Ala Gly Ala Thr Leu Glu
820 825 830

Arg Pro Lys Thr Leu Ser Pro Gly Lys Asn Gly Val Val Lys Asp Val
835 840 845

Phe Ala Phe Gly Gly Ala Val Glu Asn Pro Glu Tyr Leu Thr Pro Gln
850 855 860

Gly Gly Ala Ala Pro Gln Pro His Pro Pro Pro Ala Phe Ser Pro Ala
865 870 875 880

Phe Asp Asn Leu Tyr Tyr Trp Asp Gln Asp Pro Pro Glu Arg Gly Ala
885 890 895

Pro Pro Ser Thr Phe Lys Gly Thr Pro Thr Ala Glu Asn Pro Glu Tyr
900 905 910

Leu Gly Leu Asp Val Pro Val *
915 920

FIG. 12. (CONTINUED)

24/47

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
1 5 10 15

Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
20 25 30

Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
50 55 60

Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
65 70 75 80

Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
85 90 95

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
100 105 110

Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
115 120 125

Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser
130 135 140

Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
145 150 155 160

Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
165 170 175

Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
180 185 190

His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
195 200 205

Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
210 215 220

Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
225 230 235 240

Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
245 250 255

FIG. 13. (SEQ ID NO: 7)

25/47

His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
260 265 270

Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
275 280 285

Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
290 295 300

Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
305 310 315 320

Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
325 330 335

Pro Cys Ala Arg Val Cys Tyr Gly Leu Gly Met Glu His Leu Arg Glu
340 345 350

Val Arg Ala Val Thr Ser Ala Asn Ile Gln Glu Phe Ala Gly Cys Lys
355 360 365

Lys Ile Phe Gly Ser Leu Ala Phe Leu Pro Glu Ser Phe Asp Gly Asp
370 375 380

Pro Ala Ser Asn Thr Ala Pro Leu Gln Pro Glu Gln Leu Gln Val Phe
385 390 395 400

Glu Thr Leu Glu Glu Ile Thr Gly Tyr Leu Tyr Ile Ser Ala Trp Pro
405 410 415

Asp Ser Leu Pro Asp Leu Ser Val Phe Gln Asn Leu Gln Val Ile Arg
420 425 430

Gly Arg Ile Leu His Asn Gly Ala Tyr Ser Leu Thr Leu Gln Gly Leu
435 440 445

Gly Ile Ser Trp Leu Gly Leu Arg Ser Leu Arg Glu Leu Gly Ser Gly
450 455 460

Leu Ala Leu Ile His His Asn Thr His Leu Cys Phe Val His Thr Val
465 470 475 480

Pro Trp Asp Gln Leu Phe Arg Asn Pro His Gln Ala Leu Leu His Thr
485 490 495

Ala Asn Arg Pro Glu Asp Glu Cys Val Gly Glu Gly Leu Ala Cys His
500 505 510

FIG. 13. (CONTINUED)

26/47

Gln Leu Cys Ala Arg Gly His Cys Trp Gly Pro Gly Pro Thr Gln Cys
515 520 525

Val Asn Cys Ser Gln Phe Leu Arg Gly Gln Glu Cys Val Glu Glu Cys
530 535 540

Arg Val Leu Gln Gly Leu Pro Arg Glu Tyr Val Asn Ala Arg His Cys
545 550 555 560

Leu Pro Cys His Pro Glu Cys Gln Pro Gln Asn Gly Ser Val Thr Cys
565 570 575

Phe Gly Pro Glu Ala Asp Gln Cys Val Ala Cys Ala His Tyr Lys Asp
580 585 590

Pro Pro Phe Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro Asp Leu
595 600 605

Ser Tyr Met Pro Ile Trp Lys Phe Pro Asp Glu Glu Gly Ala Cys Gln
610 615 620

Pro Cys Pro Ile Asn Cys Thr His Ser Cys Val Asp Leu Asp Asp Lys
625 630 635 640

Gly Cys Pro Ala Glu Gln Arg Ala Ser Pro Leu Thr Ser Gln Asn Glu
645 650 655

Asp Leu Gly Pro Ala Ser Pro Leu Asp Ser Thr Phe Tyr Arg Ser Leu
660 665 670

Leu Glu Asp Asp Asp Met Gly Asp Leu Val Asp Ala Glu Glu Tyr Leu
675 680 685

Val Pro Gln Gln Gly Phe Phe Cys Pro Asp Pro Ala Pro Gly Ala Gly
690 695 700

Gly Met Val His His Arg His Arg * *
705 710 714

FIG. 13.(CONTINUED)

27/47

Met Glu Leu Ala Ala Trp Cys Arg Trp Gly Phe Leu Leu Ala Leu Leu
1 5 10 15

Pro Pro Gly Ile Ala Gly Thr Gln Val Cys Thr Gly Thr Asp Met Lys
20 25 30

Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
50 55 60

Val Pro Ala Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
65 70 75 80

Gln Gly Tyr Met Leu Ile Ala His Asn Gln Val Lys Arg Val Pro Leu
85 90 95

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Lys Tyr
100 105 110

Ala Leu Ala Val Leu Asp Asn Arg Asp Pro Gln Asp Asn Val Ala Ala
115 120 125

Ser Thr Pro Gly Arg Thr Pro Glu Gly Leu Arg Glu Leu Gln Leu Arg
130 135 140

Ser Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Arg Gly Asn Pro
145 150 155 160

Gln Leu Cys Tyr Gln Asp Met Val Leu Trp Lys Asp Val Phe Arg Lys
165 170 175

Asn Asn Gln Leu Ala Pro Val Asp Ile Asp Thr Asn Arg Ser Arg Ala
180 185 190

Cys Pro Pro Cys Ala Pro Ala Cys Lys Asp Asn His Cys Trp Gly Glu
195 200 205

Ser Pro Glu Asp Cys Gln Ile Leu Thr Gly Thr Ile Cys Thr Ser Gly
210 215 220

Cys Ala Arg Cys Lys Gly Arg Leu Pro Thr Asp Cys Cys His Glu Gln
225 230 235 240

Cys Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys
245 250 255

FIG. 14. (SEQ ID NO: 8)

28/47

Leu His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu
260 265 270

Val Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met His Asn Pro Glu Gly
275 280 285

Arg Tyr Thr Phe Gly Ala Ser Cys Val Thr Thr Cys Pro Tyr Asn Tyr
290 295 300

Leu Ser Thr Glu Val Gly Ser Cys Thr Leu Val Cys Pro Pro Asn Asn
305 310 315 320

Gln Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser
325 330 335

Lys Pro Cys Ala Arg Val Cys Tyr Gly Leu Gly Met Glu His Leu Arg
340 345 350

Gly Ala Arg Ala Ile Thr Ser Asp Asn Val Gln Glu Phe Asp Gly Cys
355 360 365

Lys Lys Ile Phe Gly Ser Leu Ala Phe Leu Pro Glu Ser Phe Asp Gly
370 375 380

Asp Pro Ser Ser Gly Ile Ala Pro Leu Arg Pro Glu Gln Leu Gln Val
385 390 395 400

Phe Glu Thr Leu Glu Glu Ile Thr Gly Tyr Leu Tyr Ile Ser Ala Trp
405 410 415

Pro Asp Ser Leu Arg Asp Leu Ser Val Phe Gln Asn Leu Arg Ile Ile
420 425 430

Arg Gly Arg Ile Leu His Asp Gly Ala Tyr Ser Leu Thr Leu Gln Gly
435 440 445

Leu Gly Ile His Ser Leu Gly Leu Arg Ser Leu Arg Glu Leu Gly Ser
450 455 460

Gly Leu Ala Leu Ile His Arg Asn Ala His Leu Cys Phe Val His Thr
465 470 475 480

Val Pro Trp Asp Gln Leu Phe Arg Asn Pro His Gln Ala Leu Leu His
485 490 495

Ser Gly Asn Arg Pro Glu Glu Asp Cys Gly Leu Glu Gly Leu Val Cys
500 505 510

FIG. 14. (CONTINUED)

29/47

Asn Ser Leu Cys Ala His Gly His Cys Trp Gly Pro Gly Pro Thr Gln
515 520 525

Cys Val Asn Cys Ser His Phe Leu Arg Gly Gln Glu Cys Val Glu Glu
530 535 540

Cys Arg Val Trp Lys Gly Leu Pro Arg Glu Tyr Val Ser Asp Lys Arg
545 550 555 560

Cys Leu Pro Cys His Pro Glu Cys Gln Pro Gln Asn Ser Ser Glu Thr
565 570 575

Cys Phe Gly Ser Glu Ala Asp Gln Cys Ala Ala Cys Ala His Tyr Lys
580 585 590

Asp Ser Ser Ser Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro Asp
595 600 605

Leu Ser Tyr Met Pro Ile Trp Lys Tyr Pro Asp Glu Glu Gly Ile Cys
610 615 620

Gln Pro Cys Pro Ile Asn Cys Thr His Ser Cys Val Asp Leu Asp Glu
625 630 635 640

Arg Gly Cys Pro Ala Glu Gln Arg Ala Ser Pro Val Thr Phe
645 650 654

FIG. 14. (CONTINUED)

30/47

ATG	GAG	CTG	GCG	GCC	TTG	TGC	CGC	TGG	GGG	CTC	CTC	CTC	GCC	CTC	45
Met	Glu	Leu	Ala	Ala	Leu	Cys	Arg	Trp	Gly	Leu	Leu	Leu	Ala	Leu	
1					5					10					15
TTG	CCC	CCC	GGA	GCC	GCG	AGC	ACC	CAA	GTG	TGC	ACC	GGC	ACA	GAC	90
Leu	Pro	Pro	Gly	Ala	Ala	Ser	Thr	Gln	Val	Cys	Thr	Gly	Thr	Asp	
						20				25					30
ATG	AAG	CTG	CGG	CTC	CCT	GCC	AGT	CCC	GAG	ACC	CAC	CTG	GAC	ATG	135
Met	Lys	Leu	Arg	Leu	Pro	Ala	Ser	Pro	Glu	Thr	His	Leu	Asp	Met	
						35				40					45
CTC	CGC	CAC	CTC	TAC	CAG	GGC	TGC	CAG	GTG	GTG	CAG	GGA	AAC	CTG	180
Leu	Arg	His	Leu	Tyr	Gln	Gly	Cys	Gln	Val	Val	Gln	Gly	Asn	Leu	
					50					55					60
GAA	CTC	ACC	TAC	CTG	CCC	ACC	AAT	GCC	AGC	CTG	TCC	TTC	CTG	CAG	225
Glu	Leu	Thr	Tyr	Leu	Pro	Thr	Asn	Ala	Ser	Leu	Ser	Phe	Leu	Gln	
					65					70					75
GAT	ATC	CAG	GAG	GTG	CAG	GGC	TAC	GTG	CTC	ATC	GCT	CAC	AAC	CAA	270
Asp	Ile	Gln	Glu	Val	Gln	Gly	Tyr	Val	Leu	Ile	Ala	His	Asn	Gln	
					80					85					90
GTG	AGG	CAG	GTC	CCA	CTG	CAG	AGG	CTG	CGG	ATT	GTG	CGA	GGC	ACC	315
Val	Arg	Gln	Val	Pro	Leu	Gln	Arg	Leu	Arg	Ile	Val	Arg	Gly	Thr	
					95					100					105
CAG	CTC	TTT	GAG	GAC	AAC	TAT	GCC	CTG	GCC	GTG	CTA	GAC	AAT	GGA	360
Gln	Leu	Phe	Glu	Asp	Asn	Tyr	Ala	Leu	Ala	Val	Leu	Asp	Asn	Gly	
					110					115					120
GAC	CCG	CTG	AAC	AAT	ACC	ACC	CCT	GTC	ACA	GGG	GCC	TCC	CCA	GGA	405
Asp	Pro	Leu	Asn	Asn	Thr	Thr	Pro	Val	Thr	Gly	Ala	Ser	Pro	Gly	
					125					130					135
GGC	CTG	CGG	GAG	CTG	CAG	CTT	CGA	AGC	CTC	ACA	GAG	ATC	TTG	AAA	450
Gly	Leu	Arg	Glu	Leu	Gln	Leu	Arg	Ser	Leu	Thr	Glu	Ile	Leu	Lys	
					140					145					150
GGA	GGG	GTC	TTG	ATC	CAG	CGG	AAC	CCC	CAG	CTC	TGC	TAC	CAG	GAC	495
Gly	Gly	Val	Leu	Ile	Gln	Arg	Asn	Pro	Gln	Leu	Cys	Tyr	Gln	Asp	
					155					160					165
ACG	ATT	TTG	TGG	AAG	GAC	ATC	TTC	CAC	AAG	AAC	AAC	CAG	CTG	GCT	540
Thr	Ile	Leu	Trp	Lys	Asp	Ile	Phe	His	Lys	Asn	Asn	Gln	Leu	Ala	
					170					175					180

FIG. 15. (SEQ ID NO:9)

CTC	ACA	CTG	ATA	GAC	ACC	AAC	CGC	TCT	CGG	GCC	TGC	CAC	CCC	TGT	585
Leu	Thr	Leu	Ile	Asp	Thr	Asn	Arg	Ser	Arg	Ala	Cys	His	Pro	Cys	
															195
															185
															190
TCT	CCG	ATG	TGT	AAG	GGC	TCC	CGC	TGC	TGG	GGA	GAG	AGT	TCT	GAG	630
Ser	Pro	Met	Cys	Lys	Gly	Ser	Arg	Cys	Trp	Gly	Glu	Ser	Ser	Glu	
															210
															200
															205
GAT	TGT	CAG	AGC	CTG	ACG	CGC	ACT	GTC	TGT	GCC	GGT	GGC	TGT	GCC	675
Asp	Cys	Gln	Ser	Leu	Thr	Arg	Thr	Val	Cys	Ala	Gly	Gly	Cys	Ala	
															225
															215
															220
CGC	TGC	AAG	GGG	CCA	CTG	CCC	ACT	GAC	TGC	TGC	CAT	GAG	CAG	TGT	720
Arg	Cys	Lys	Gly	Pro	Leu	Pro	Thr	Asp	Cys	Cys	His	Glu	Gln	Cys	
															230
															235
															240
GCT	GCC	GGC	TGC	ACG	GGC	CCC	AAG	CAC	TCT	GAC	TGC	CTG	GCC	TGC	765
Ala	Ala	Gly	Cys	Thr	Gly	Pro	Lys	His	Ser	Asp	Cys	Leu	Ala	Cys	
															245
															250
															255
CTC	CAC	TTC	AAC	CAC	AGT	GGC	ATC	TGT	GAG	CTG	CAC	TGC	CCA	GCC	810
Leu	His	Phe	Asn	His	Ser	Gly	Ile	Cys	Glu	Leu	His	Cys	Pro	Ala	
															260
															265
															270
CTG	GTC	ACC	TAC	AAC	ACA	GAC	ACG	TTT	GAG	TCC	ATG	CCC	AAT	CCC	855
Leu	Val	Thr	Tyr	Asn	Thr	Asp	Thr	Phe	Glu	Ser	Met	Pro	Asn	Pro	
															275
															280
															285
GAG	GGC	CGG	TAT	ACA	TTC	GGC	GCC	AGC	TGT	GTG	ACT	GCC	TGT	CCC	900
Glu	Glu	Arg	Tyr	Thr	Phe	Gly	Ala	Ser	Cys	Val	Thr	Ala	Cys	Pro	
															290
															295
															300
TAC	AAC	TAC	CTT	TCT	ACG	GAC	GTG	GGA	TCC	TGC	ACC	CTC	GTC	TGC	945
Tyr	Asn	Tyr	Leu	Ser	Thr	Asp	Val	Gly	Ser	Cys	Thr	Leu	Val	Cys	
															305
															310
															315
CCC	CTG	CAC	AAC	CAA	GAG	GTG	ACA	GCA	GAG	GAT	GGA	ACA	CAG	CGG	990
Pro	Leu	His	Asn	Gln	Glu	Val	Thr	Ala	Glu	Asp	Gly	Thr	Gln	Arg	
															320
															325
															330
TGT	GAG	AAG	TGC	AGC	AAG	CCC	TGT	GCC	CGA	GTG	TGC	TAT	GGT	CTG	1035
Cys	Glu	Lys	Cys	Ser	Lys	Pro	Cys	Ala	Arg	Val	Cys	Tyr	Gly	Leu	
															335
															340
															345
GGC	ATG	GAG	CAC	TTG	CGA	GAG	GTG	AGG	GCA	GTT	ACC	AGT	GCC	AAT	1080
Gly	Met	Glu	His	Leu	Arg	Glu	Val	Arg	Ala	Val	Thr	Ser	Ala	Asn	
															350
															355
															360

FIG. 15. (CONTINUED)

32/47

FIG. 15. (CONTINUED)

GTG GAG GAA TGC CGA GTA CTG CAG GGG CTC CCC AGG GAG TAT GTG 1665
 Val Glu Glu Cys Arg Val Leu Gln Gly Leu Pro Arg Glu Tyr Val
 545 550 555

AAT GCC AGG CAC TGT TTG CCG TGC CAC CCT GAG TGT CAG CCC CAG 1710
 Asn Ala Arg His Cys Leu Pro Cys His Pro Glu Cys Gln Pro Gln
 560 565 570

AAT GGC TCA GTG ACC TGT TTT GGA CCG GAG GCT GAC CAG TGT GTG 1755
 Asn Gly Ser Val Thr Cys Phe Gly Pro Glu Ala Asp Gln Cys Val
 575 580 585

GCC TGT GCC CAC TAT AAG GAC CCT CCC TTC TGC GTG GCC CGC TGC 1800
 Ala Cys Ala His Tyr Lys Asp Pro Pro Phe Cys Val Ala Arg Cys
 590 595 600

CCC AGC GGT GTG AAA CCT GAC CTC TCC TAC ATG CCC ATC TGG AAG 1845
 Pro Ser Gly Val Lys Pro Asp Leu Ser Tyr Met Pro Ile Trp Lys
 605 610 615

TTT CCA GAT GAG GAG GGC GCA TGC CAG CCT TGC CCC ATC AAC TGC 1890
 Phe Pro Asp Glu Glu Gly Ala Cys Gln Pro Cys Pro Ile Asn Cys
 620 625 630

ACC CAC TCC TGT GTG GAC CTG GAT GAC AAG GGC TGC CCC GCC GAG 1935
 Thr His Ser Cys Val Asp Leu Asp Asp Lys Gly Cys Pro Ala Glu
 635 640 645

CAG AGA GCC AGC CCT CTG ACG TCC ATC ATC TCT GCG GTG GTT GGC 1980
 Gln Arg Ala Ser Pro Leu Thr Ser Ile Ile Ser Ala Val Val Gly
 650 655 660

ATT CTG CTG GTC GTG GTC TTG GGG GTG GTC TTT GGG ATC CTC ATC 2025
 Ile Leu Leu Val Val Val Leu Gly Val Val Phe Gly Ile Leu Ile
 665 670 675

AAG CGA CGG CAG CAG AAG ATC CGG AAG TAC ACG ATG CGG AGA CTG 2070
 Lys Arg Arg Gln Gln Lys Ile Arg Lys Tyr Thr Met Arg Arg Leu
 680 685 690

CTG CAG GAA ACG GAG CTG GTG GAG CCG CTG ACA CCT AGC GGA GCG 2115
 Leu Gln Glu Thr Glu Leu Val Glu Pro Leu Thr Pro Ser Gly Ala
 695 700 705

ATG CCC AAC CAG GCG CAG ATG CGG ATC CTG AAA GAG ACG GAG CTG 2160
 Met Pro Asn Gln Ala Gln Met Arg Ile Leu Lys Glu Thr Glu Leu
 710 715 720

FIG. 15. (CONTINUED)

34/47

AGG AAG GTG AAG GTG CTT GGA TCT GGC GCT TTT GGC ACA GTC TAC 2205
 Arg Lys Val Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr
 725 730 735

AAG GGC ATC TGG ATC CCT GAT GGG GAG AAT GTG AAA ATT CCA GTG 2250
 Lys Gly Ile Trp Ile Pro Asp Gly Glu Asn Val Lys Ile Pro Val
 740 745 750

GCC ATC AAA GTG TTG AGG GAA AAC ACA TCC CCC AAA GCC AAC AAA 2295
 Ala Ile Lys Val Leu Arg Glu Asn Thr Ser Pro Lys Ala Asn Lys
 755 760 765

GAA ATC TTA GAC GAA GCA TAC GTG ATG GCT GGT GTG GGC TCC CCA 2340
 Glu Ile Leu Asp Glu Ala Tyr Val Met Ala Gly Val Gly Ser Pro
 770 775 780

TAT GTC TCC CGC CTT CTG GGC ATC TGC CTG ACA TCC ACG GTG CAG 2385
 Tyr Val Ser Arg Leu Leu Gly Ile Cys Leu Thr Ser Thr Val Gln
 785 790 795

CTG GTG ACA CAG CTT ATG CCC TAT GGC TGC CTC TTA GAC CAT GTC 2430
 Leu Val Thr Gln Leu Met Pro Tyr Gly Cys Leu Leu Asp His Val
 800 805 810

CGG GAA AAC CGC GGA CGC CTG GGC TCC CAG GAC CTG CTG AAC TGG 2475
 Arg Glu Asn Arg Gly Arg Leu Gly Ser Gln Asp Leu Leu Asn Trp
 815 820 825

TGT ATG CAG ATT GCC AAG GGG ATG AGC TAC CTG GAG GAT GTG CGG 2520
 Cys Met Gln Ile Ala Lys Gly Met Ser Tyr Leu Glu Asp Val Arg
 830 835 840

CTC GTA CAC AGG GAC TTG GCC GCT CGG AAC GTG CTG GTC AAG AGT 2565
 Leu Val His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Lys Ser
 845 850 855

CCC AAC CAT GTC AAA ATT ACA GAC TTC GGG CTG GCT CGG CTG CTG 2610
 Pro Asn His Val Lys Ile Thr Asp Phe Gly Leu Ala Arg Leu Leu
 860 865 870

GAC ATT GAC GAG ACA GAG TAC CAT GCA GAT GGG GGC AAG GTG CCC 2655
 Asp Ile Asp Glu Thr Glu Tyr His Ala Asp Gly Gly Lys Val Pro
 875 880 885

ATC AAG TGG ATG GCG CTG GAG TCC ATT CTC CGC CGG CGG TTC ACC 2700
 Ile Lys Trp Met Ala Leu Glu Ser Ile Leu Arg Arg Arg Phe Thr
 890 895 900

FIG. 15. (CONTINUED)

35/47

CAC CAG AGT GAT GTG TGG AGT TAT GGT GTG ACT GTG TGG GAG CTG 2745
 His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Val Trp Glu Leu
 905 910 915

ATG ACT TTT GGG GCC AAA CCT TAC GAT GGG ATC CCA GCC CGG GAG 2790
 Met Thr Phe Gly Ala Lys Pro Tyr Asp Gly Ile Pro Ala Arg Glu
 920 925 930

ATC CCT GAC CTG CTG GAA AAG GGG GAG CGG CTG CCC CAG CCC CCC 2835
 Ile Pro Asp Leu Leu Glu Lys Lgy Glu Arg Leu Pro Gln Pro Pro
 935 940 945

ATC TGC ACC ATT GAT GTC TAC ATG ATC ATG GTC AAA TGT TGG ATG 2880
 Ile Cys Thr Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp Met
 950 955 960

ATT GAC TCT GAA TGT CGG CCA AGA TTC CGG GAG TTG GTG TCT GAA 2925
 Ile Asp Ser Glu Cys Arg Pro Arg Phe Arg Glu Leu Val Ser Glu
 965 970 975

TTC TCC CGC ATG GCC AGG GAC CCC CAG CGC TTT GTG GTC ATC CAG 2970
 Phe Ser Arg Met Ala Arg Asp Pro Gln Arg Phe Val Val Ile Gln
 980 985 990

AAT GAG GAC TTG GGC CCA GCC AGT CCC TTG GAC AGC ACC TTC TAC 3015
 Asn Glu Asp Leu Gly Pro Ala Ser Pro Leu Asp Ser Thr Phe Tyr
 995 1000 1005

CGC TCA CTG CTG GAG GAC GAT GAC ATG GGG GAC CTG GTG GAT GCT 3060
 Arg Ser Leu Leu Glu Asp Asp Asp Met Gly Asp Leu Val Asp Ala
 1010 1015 1020

GAG GAG TAT CTG GTA CCC CAG CAG GGC TTC TTC TGT CCA GAC CCT 3105
 Glu Glu Tyr Leu Val Pro Gln Gln Gly Phe Phe Cys Pro Asp Pro
 1025 1030 1035

GCC CCG GGC GCT GGG GGC ATG GTC CAC CAC AGG CAC CGC AGC TCA 3150
 Ala Pro Gly Ala Gly Gly Met Val His His Arg His Arg Ser Ser
 1040 1045 1050

TCT ACC AGG AGT GGC GGT GGG GAC CTG ACA CTA GGG CTG GAG CCC 3195
 Ser Thr Arg Ser Gly Gly Asp Leu Thr Leu Gly Leu Glu Pro
 1055 1060 1065

TCT GAA GAG GAG GCC CCC AGG TCT CCA CTG GCA CCC TCC GAA GGG 3240
 Ser Glu Glu Glu Ala Pro Arg Ser Pro Leu Ala Pro Ser Glu Gly
 1070 1075 1080

FIG. 15. (CONTINUED)

36/47

FIG. 15. (CONTINUED)

ccggggccgga gccgcaatga tcatcatgga gctggcggcc tggtgccgct 50
 gggggttcct cctcgccctc ctgccccccg gaatcgccgg cacccaagtg 100
 tgtaccggca cagacatgaa gttgcggctc cctgccaatgc ctgagaccca 150
 cctggacatg ctccgcccacc tgtaccaggg ctgtcaggtt gtgcaggggca 200
 acttggagct tacctacgtt cctgccaatg ccagcctctc attcctgcag 250
 gacatccagg aagttcaggg ttacatgctc atcgctcaca accaggtgaa 300
 gcgcgtccca ctgcaaaggc tgcgcacatgt gagagggacc cagctcttg 350
 aggacaagta tgccctggct gtgctagaca accgagatcc tcaggacaat 400
 gtcgcccctt ccaccccagg cagaacccca gaggggctgc gggagctgca 450
 gttcgaagt ctcacagaga tcctgaaggg aggagtttg atccgtggaa 500
 accctcagct ctgctaccag gacatggttt tgtggaaagga cgtctccgc 550
 aagaataacc aactggctcc tgtcgatata gacaccaatc gttcccggc 600
 ctgtccaccc ttgtccccccg cctgcaaaga caatcactgt tgggtgaga 650
 gtccggaaaga ctgtcagatc ttgactggca ccatctgtac cagtggttgt 700
 gcccggtgca agggccggct gcccactgac tgctgccatg agcagtgtgc 750
 cgcaggctgc acggggccca agcattctga ctgcctggcc tgcctccact 800
 tcaatcatag ttgtatctgt gagctgcact gcccagccct cgtcacctac 850
 aacacagaca cctttgagtc catgcacaac cctgagggtc gctacaccc 900
 tggtgccagc tgcgtgacca cctgccccta caactacctg tctacggaag 950
 tgggatcctg cactctggtg ttgtccccca ataaccaaga ggtcacagct 1000
 gaggacggaa cacagcgtt tgagaaatgc agcaagccct gtgctcgagt 1050
 gtgctatggt ctgggcatgg agcaccttcg aggggcgagg gccatcacca 1100
 gtgacaatgt ccaggagttt gatggctgca agaagatctt tgggagcctg 1150
 gcattttgc cggagagctt tgatggggac ccctcctccg gcattgctcc 1200
 gctgaggccct gagcagctcc aagtgttgcg aaccctggag gagatcacag 1250
 gttacctgtt catctcagca tggccagaca gtctccgtga cctcagtgtc 1300
 ttccagaacc ttcgaatcat tcggggacgg attctccacg atggcgctga 1350
 ctcattgaca ctgcaaggcc tggggatcca ctgcgtgggg ctgcgctcac 1400
 tgcggagct gggcagtgga ttggctctga ttcaccgcaa cgcccatctc 1450
 tgctttgtac acactgtacc ttgggaccag ctcttcggg acccacatca 1500
 ggccctgctc cacagtggga accggccgga agaggactt tgctctcg 1550
 gcggcttggt ctgtaactca ctgtgtgccc acgggcactg ctgggggcca 1600
 gggcccaccc agtgtgtcaa ctgcagtcat ttccctcggg gccaggagt 1650
 tgtggaggag tgccgagttt ggaagggct ccccccggag tatgtgagtg 1700
 acaagcgctg tctgcccgtgt caccccgagt gtcagccctca aaacagctca 1750
 gagacctgtt ttggatcgga ggctgatcag tgtgcagcct ggcggccacta 1800
 caaggactcg tcctccctgt tggctcgctg ccccagtgggt gtgaaaccgg 1850
 acctctccatc catgcccattc tggaaatacc cggatgagga gggcatatgc 1900
 cagccgtgcc ccatcaactg caccactcc tggatggatc tggatgaacg 1950
 aggctgccccca gcagagcaga gagccagccc ggtgacattc atcattgcaa 2000
 ctgttagaggg cgtcctgctg ttccctgatct tagtgggttgt cggttggaaatc 2050
 ctaatcaaacc gaaggagaca gaagatccgg aagtatacga tgcgttagct 2100
 gctgcaggaa actgagttt tagtggatggct gacgcccagc ggagcaatgc 2150
 ccaaccaggc tcagatgcgg atcctaaaag agacggagct aaggaagggtg 2200
 aaggtgcttg gatcaggagc ttggatggact gtctacaagg gcatctgat 2250
 cccagatggg gagaatgtga aaatccccgt ggctatcaag gtgttgagag 2300
 aaaacacatc tcctaaagcc aacaaagaaa ttcttagatga agcgtatgtg 2350

FIG. 16. (SEQ ID NO: 10)

atggctggtg tgggttctcc gtatgtgtcc cgccctcctgg gcatctgcct 2400
 gacatccaca gtacagctgg tgacacagct tatgccctac ggctgcctc 2450
 tggaccatgt ccgagaacac cgaggtcgcc taggctccca ggacctgctc 2500
 aactggtgtg ttcagattgc caaggggatg agctacctgg aggacgtgcg 2550
 gcttgtacac agggacctgg ctgcccggaa tgtgctagtc aagagtccca 2600
 accacgtcaa gattacagat ttcgggctgg ctcggctgct ggacattgtat 2650
 gagacagagt accatgcaga tggggcaag gtgcccattca aatggatggc 2700
 attggaatct attctcagac gccgggttac ccattcagagt gatgtgtgga 2750
 gctatggagt gactgtgtgg gagctgatga cttttgggc caaaccttac 2800
 gatggaatcc cagccccggaa gatccctgat ttgctggaga agggagaacg 2850
 cctacccatcg cctccaaatct gcaccattga tgtctacatg attatggtca 2900
 aatgttggat gattgactct gaatgtcgcc cgagattccg ggagttggtg 2950
 tcagaatttt cacgtatggc gagggacccc cagcggtttg tggtcatcca 3000
 gaacgaggac ttggggccat ccagccccat ggacagtacc ttctaccgtt 3050
 cactgctgga agatgatgac atgggtgacc tggtagacgc tgaagagtat 3100
 ctggtgcccc agcaggatt cttctccccg gaccctaccc caggcactgg 3150
 gagcacagcc catagaaggc accgcagctc gtccaccagg agtggaggtg 3200
 gtgagctgac actgggcctg gagccctcg aagaagggcc ccccaagatct 3250
 ccactggctc cctcggaaagg ggctggctcc gatgtgtttg atggtgacct 3300
 ggcaatgggg gtaaccaaag ggctgcagag cctctcttca catgacctca 3350
 gccccttaca gcggtacagc gaggacccc cattacctt gccccccgag 3400
 actgatggct atgttgcctc cttggcctgc agccccccagc ccgagttatgt 3450
 gaaccaatca gaggttcagc ctcagcctcc ttaacccc gagggtcctc 3500
 tgcctcctgt ccggcctgct ggtgctactc tagaaagacc caagactctc 3550
 tctcctggga agaatgggt tgtcaaagac gttttgcct tcgggggtgc 3600
 tgtggagaac cctgaataact tagtaccgag agaaggcact gcctctccgc 3650
 cccacccttc tcctgccttc agcccagcct ttgacaacct ctattactgg 3700
 gaccagaact catcgagca ggggcctcca ccaagtaact ttgaaggac 3750
 ccccaactgca gagaaccctg agtacctagg cctggatgta cctgtatgag 3800
 acgtgtgcag acgtcctgtg ctttcagagt ggggaaggcc tgacttggtgg 3850
 tctccatcgc cacaacgcag ggagagggtc ctctggccac attacatcca 3900
 gggcagacgg ctctaccagg aacctgcccc gaggaacctt tccttgctgc 3850
 ttgaa 3955

FIG. 16. (CONTINUED)

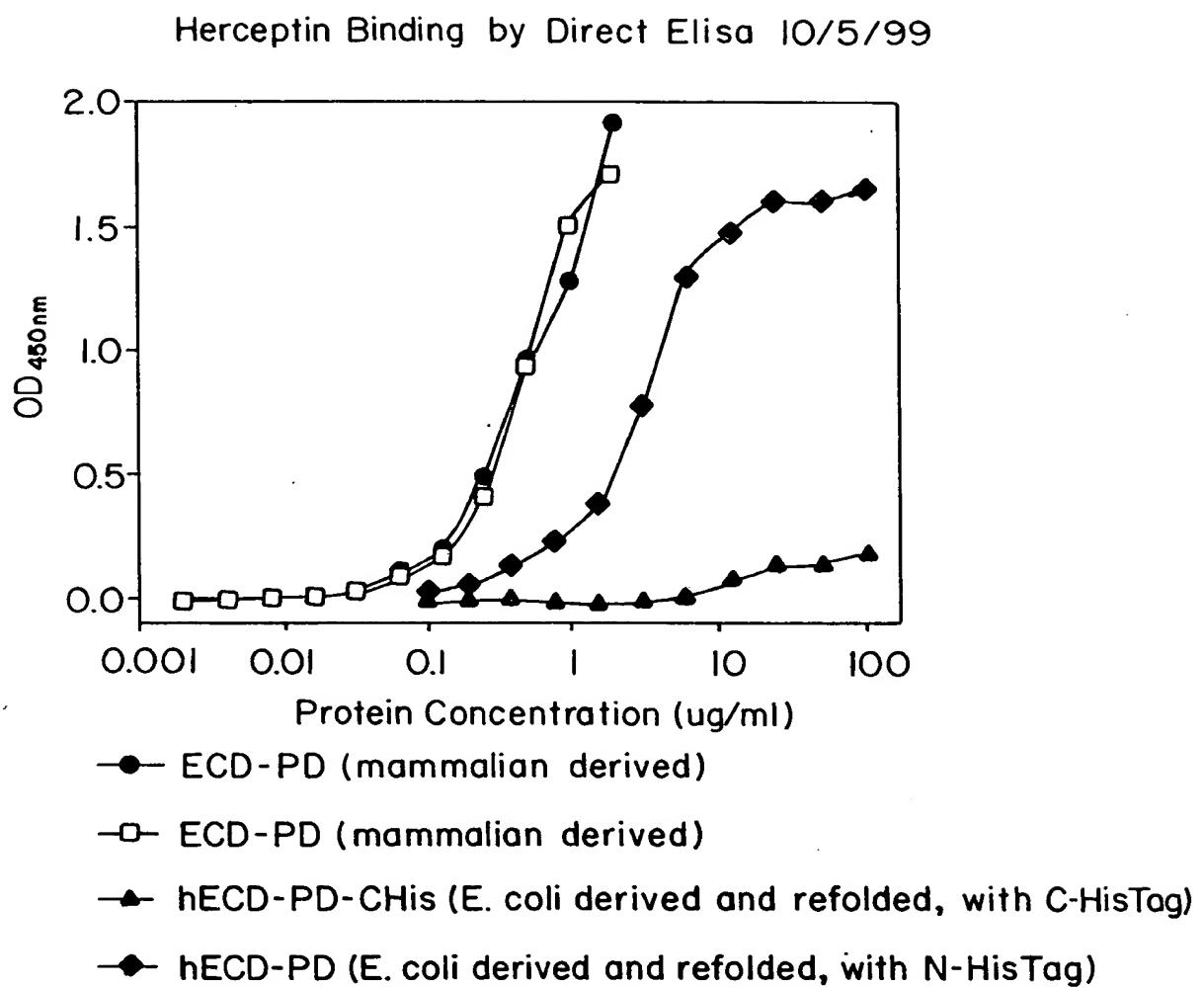
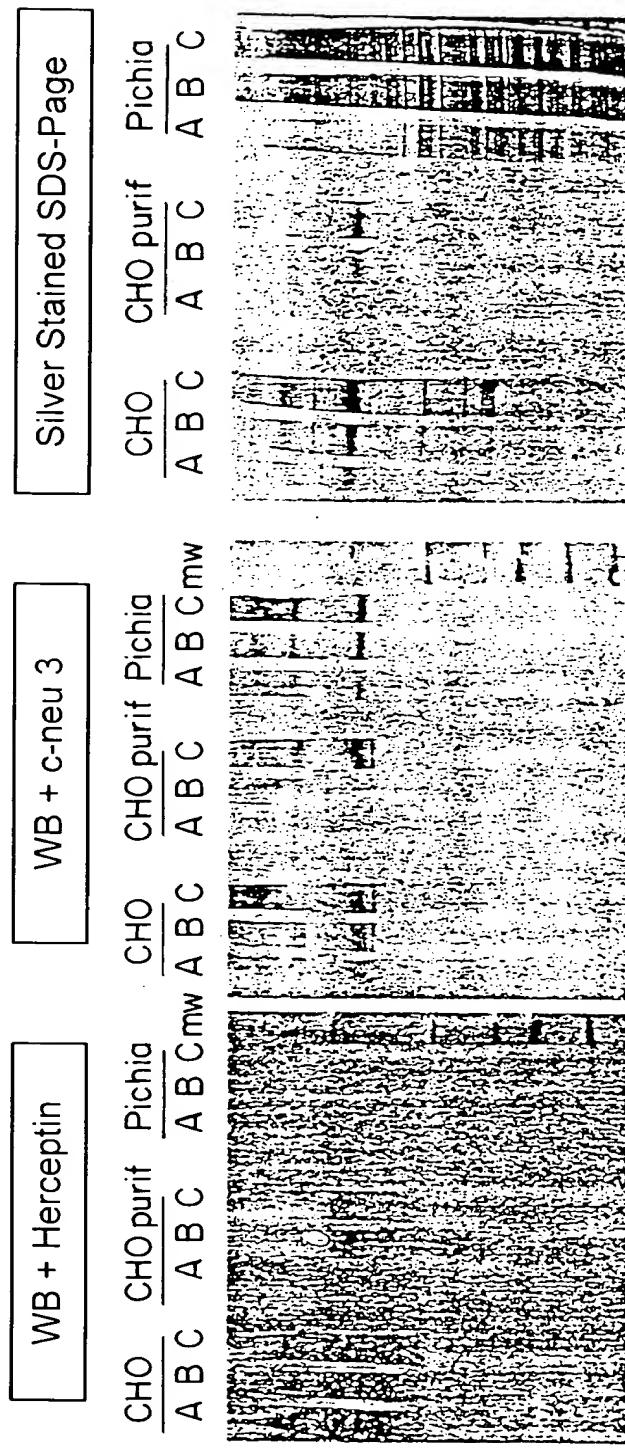


FIG. 17.

Comparison of Her2neu ECD-PD Expression in CHO-K1 (S/SF) and Pichia (Non reducing conditions)



Legend: CHO; A, B, C = 2,5 μ l/ 5 μ l/ 10 μ l
 CHO purif; A, B, C = 125ng/ 250ng/ 500ng
 Pichia; A, B, C = 2,5 μ l/ 5 μ l/ 10 μ l from a 1/30 dilution of OD 120

FIG. 18.

atggagctgg cggcctggtg cggttgggg ttcctcctcg ccctcctgtc 50
 ccccggagcc gcgggtaccc aagtgtgtac cggtaccgac atgaagttgc 100
 gactccctgc cagtcctgag acccacctgg acatgcttcg ccacctctac 150
 cagggctgtc aggtggtgca gggcaattt gagttaccc acctgcccgc 200
 caatgccagc ctctcattcc tgcaggacat ccaggaagtc cagggataca 250
 tgctcatcgc tcacaaccga gtgaaacacg tcccactgca gaggttgcg 300
 atcgtgagag ggactcagct ctttggggac aagtatgccc tggctgtgct 350
 agacaaccga gaccctttgg acaacgtcac caccgcccgc ccaggcagaa 400
 ccccagaagg gctgcgggag ctgcagcttc gaagtctcac agagatctt 450
 aaggaggag ttttgcattcg tgggaaccct cagctctgct accaggacat 500
 ggttttgtgg aaggatgtcc tccgtaaagaa taaccagctg gctcctgtcg 550
 acatggacac caatcgttcc cgggcctgtc caccttgcgc cccaacctgc 600
 aaagacaatc actgttgggg tgagagtcct gaagactgtc agatcttgc 650
 tggcaccatc tgtacttagt gctgtgcccgt gtgcaagggc cggctgccc 700
 ctgactgttgc ccatgagcag tgtgctgcag gctgcacccgg tcccaagcat 750
 tctgactgtcc tggcctgcct ccacttcaat catagtggta tctgtgagct 800
 gcactgcccgg gcccctcatca cctacaacac agacacccctc gagtccatgc 850
 tcaaccctga gggtcgtcac acctttgggtg ccagctgtgt gaccacctgc 900
 ccctacaact acctctccac ggaagtggga tcctgcactc tggctgtcc 950
 cccgaacaacaa caagaggtca cagctgagga cggAACACAG cgggtgtgaga 1000
 aatgcagcaa gcccctgtct ggagtatgtct atggctgtgg catggagcac 1050
 ctccgagggg cggggccat caccagtgc aatatccagg agtttgctgg 1100
 ctgcaagaag atctttggga gcctggcatt tttgccggag agctttgtatg 1150
 ggaaccctc ctccggcgtt gccccactga agccagagca tctccaagtg 1200
 ttcgaaaccc tggaggagat cacaggttac ctatacattt cagcatggcc 1250
 agagagcttc caagacacta gtgtcttcca gaaccttcgg gtcattcggg 1300
 gacggattct ccatgatggt gcttactcat tgacgttgca aggctgggg 1350
 attcactcac tggggctacg ctcactgcgg gagctggca gtggattggc 1400
 tctcattcac cgcaacaccc atctctgttt tggtaaacact gtaccttggg 1450
 accagctctt cccggAACCCG caccaggccc tactccacag tgggaaccgg 1500
 ccagaagagg catgtggctt tgagggcttg gtctgtact cactgtgtgc 1550
 ccgtggcacc tgctggggc caggcccac ccagttgttc aactgcagtc 1600
 agttccctccg gggccaggag tgtgtggagg agtgcggagt atggaaagggg 1650
 ctccccaggg agtatgtgag gggcaagcac tgcgtccat gccaccccg 1700
 gtgtcagccct caaaacagct cggagacctg ctatggatcg gaggctgacc 1750
 agtgtgaggc ttgtgcccac tacaaggact catcttctg tggctcgc 1800
 tgccccagtg gtgtgaagcc agacctctcc tacatgccta tctggaaagta 1850
 cccggatgag gaggccatcat gtcagccatg ccccatcaac tgcacccact 1900
 catgtgtggc cctggacgaa cgaggctgcc cagcagagca gagagccagc 1950
 ccagtgacat tcatttcgtc aactgtggtg ggcgtccgt tgttcctgtat 2000
 catagtggc gtcattggaa tcctaataaa acgaaggcga cagaagatcc 2050
 ggaagtatac catgcgttagg ctgctgcagg agaccgagct ggtggagccg 2100
 ctgacgccc gttggagctgt gcccAACCCAG gctcagatgc ggatcctaaa 2150
 ggagacagag ctaaggaagc tgaaggtgct tgggtcagga gccttcggca 2200
 ctgtctacaa gggcatctgg atcccagatg gggagaacgt gaaaatcccc 2250
 gtggccatca aggtgttgag ggaaaacaca ttcctaaag ctaacaaaga 2300
 aatcctagat gaagcgtacg tcatggctgg tgggttct ccatatgtt 2350

FIG. 19. (SEQ ID NO: 11)

cccgcctcct gggcatctgc ctgacatcca cagtgcagct ggtgacacag 2400
 cttatgccct atggctgcct tctggaccat gtccgagaac accgaggctg 2450
 cttaggctcc caggacactgc tcaactggtg tgttcagatt gccaagggg 2500
 tgagctacct ggaggaagtt cggcttggc acagggacct agctgcccga 2550
 aacgtgctag tcaagagtcc caaccacgtc aagattaccg acttcgggct 2600
 ggcacggctg ctggacattg atgagactga ataccatgca gatggggca 2650
 aggtgcccat caagtggatg gcattggaat ctattctcag acgcccggtc 2700
 actcatcaga gtgatgtgtg gagctatggt gtgactgtgt gggagctgat 2750
 gacctttggg gccaaacctt acgatggat cccagctcgg gagatccctg 2800
 atttgctgga gaagggagaa cgcctacctc agcctccaat ctgcaccatc 2850
 gacgtctaca tgatcatggt caaatgttgg atgattgact ccgaatgtcg 2900
 cccgagattc cgggaggtgg tattcagaatt ctcccgatg gcaagggacc 2950
 cccagcgctt tgggtcatac cagaacgagg acttagggcc ctccagcccc 3000
 atggacagca ccttctaccg ttcactgctg gaggatgatg acatgggg 3050
 gctggtcgtat gctgaagagt acctggtacc ccagcaggga ttcttctccc 3100
 cagaccctgc ccttaggtact gggagcacag cccaccgcag acaccgcagc 3150
 tcgtcggcca ggagtggcg 2999 tggtagctg acactggcc tggagccctc 3200
 ggaagaagag ccccccagat ctccactggc tccctccgaa ggggctggct 3250
 ccgatgtgtt tgatggtgac ctggcagtgg gggtaaccaa aggactgcag 3300
 agcctctctc cacatgaccc tggccctcta cagcggtaca gtgaggatcc 3350
 cacattacct ctgccccccg agactgatgg ctacggttgc cccctggct 3400
 gcagccccca gcccggatgtat gtgaaccagc cagaggttcg gcctcagtt 3450
 cccttgaccc cagagggtcc tccgcctccc atccgacccg ctggtgctac 3500
 tctagaaaaga cccaaagactc tcttcctgg gaaaaatggg gttgtcaaag 3550
 acgtttttgc ctgggggggt gctgtggaga accctgaata cctagcaccc 3600
 agagcaggca ctgcctctca gccccaccct tctcctgcct tcagcccgac 3650
 ctggacaac ctctattact gggaccagaa ctcatcgag cagggtcctc 3700
 caccaaatgtac ctggaaaggg acccccactg cagagaaccc tgagtaccta 3750
 ggcctggatg tgccagatgt a 3771

FIG. 19.(CONTINUED)

43/47

Met Glu Leu Ala Ala Trp Cys Arg Trp Gly Phe Leu Leu Ala Leu Leu
1 5 10 15

Ser Pro Gly Ala Ala Gly Thr Gln Val Cys Thr Gly Thr Asp Met Lys
20 25 30

Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
50 55 60

Leu Pro Ala Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
65 70 75 80

Gln Gly Tyr Met Leu Ile Ala His Asn Arg Val Lys His Val Pro Leu
85 90 95

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Lys Tyr
100 105 110

Ala Leu Ala Val Leu Asp Asn Arg Asp Pro Leu Asp Asn Val Thr Thr
115 120 125

Ala Ala Pro Gly Arg Thr Pro Glu Gly Leu Arg Glu Leu Gln Leu Arg
130 135 140

Ser Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Arg Gly Asn Pro
145 150 155 160

Gln Leu Cys Tyr Gln Asp Met Val Leu Trp Lys Asp Val Leu Arg Lys
165 170 175

Asn Asn Gln Leu Ala Pro Val Asp Met Asp Thr Asn Arg Ser Arg Ala
180 185 190

Cys Pro Pro Cys Ala Pro Thr Cys Lys Asp Asn His Cys Trp Gly Glu
195 200 205

Ser Pro Glu Asp Cys Gln Ile Leu Thr Gly Thr Ile Cys Thr Ser Gly
210 215 220

Cys Ala Arg Cys Lys Gly Arg Leu Pro Thr Asp Cys Cys His Glu Gln
225 230 235 240

Cys Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys
245 250 255

FIG. 20. (SEQ ID NO: 14)

44/47

Leu His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu
260 265 270

Ile Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Leu Asn Pro Glu Gly
275 280 285

Arg Tyr Thr Phe Gly Ala Ser Cys Val Thr Thr Cys Pro Tyr Asn Tyr
290 295 300

Leu Ser Thr Glu Val Gly Ser Cys Thr Leu Val Cys Pro Pro Asn Asn
305 310 315 320

Gln Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser
325 330 335

Lys Pro Cys Ala Gly Val Cys Tyr Gly Leu Gly Met Glu His Leu Arg
340 345 350

Gly Ala Arg Ala Ile Thr Ser Asp Asn Ile Gln Glu Phe Ala Gly Cys
355 360 365

Lys Lys Ile Phe Gly Ser Leu Ala Phe Leu Pro Glu Ser Phe Asp Gly
370 375 380

Asn Pro Ser Ser Gly Val Ala Pro Leu Lys Pro Glu His Leu Gln Val
385 390 395 400

Phe Glu Thr Leu Glu Glu Ile Thr Gly Tyr Leu Tyr Ile Ser Ala Trp
405 410 415

Pro Glu Ser Phe Gln Asp Leu Ser Val Phe Gln Asn Leu Arg Val Ile
420 425 430

Arg Gly Arg Ile Leu His Asp Gly Ala Tyr Ser Leu Thr Leu Gln Gly
435 440 445

Leu Gly Ile His Ser Leu Gly Leu Arg Ser Leu Arg Glu Leu Gly Ser
450 455 460

Gly Leu Ala Leu Ile His Arg Asn Thr His Leu Cys Phe Val Asn Thr
465 470 475 480

Val Pro Trp Asp Gln Leu Phe Arg Asn Pro His Gln Ala Leu Leu His
485 490 495

Ser Gly Asn Arg Pro Glu Glu Ala Cys Gly Leu Glu Gly Leu Val Cys
500 505 510

FIG. 20. (CONTINUED)

45/47

Asn Ser Leu Cys Ala Arg Gly His Cys Trp Gly Pro Gly Pro Thr Gln
515 520 525

Cys Val Asn Cys Ser Gln Phe Leu Arg Gly Gln Glu Cys Val Glu Glu
530 535 540

Cys Arg Val Trp Lys Gly Leu Pro Arg Glu Tyr Val Arg Gly Lys His
545 550 555 560

Cys Leu Pro Cys His Pro Glu Cys Gln Pro Gln Asn Ser Ser Glu Thr
565 570 575

Cys Tyr Gly Ser Glu Ala Asp Gln Cys Glu Ala Cys Ala His Tyr Lys
580 585 590

Asp Ser Ser Ser Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro Asp
595 600 605

Leu Ser Tyr Met Pro Ile Trp Lys Tyr Pro Asp Glu Glu Gly Ile Cys
610 615 620

Gln Pro Cys Pro Ile Asn Cys Thr His Ser Cys Val Asp Leu Asp Glu
625 630 635 640

Arg Gly Cys Pro Ala Glu Gln Arg Ala Ser Pro Val Thr Phe Ile Ile
645 650 655

Ala Thr Val Val Gly Val Leu Leu Phe Leu Ile Ile Val Val Val Ile
660 665 670

Gly Ile Leu Ile Lys Arg Arg Gln Lys Ile Arg Lys Tyr Thr Met
675 680 685

Arg Arg Leu Leu Gln Glu Thr Glu Leu Val Glu Pro Leu Thr Pro Ser
690 695 700

Gly Ala Val Pro Asn Gln Ala Gln Met Arg Ile Leu Lys Glu Thr Glu
705 710 715 720

Leu Arg Lys Leu Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr
725 730 735

Lys Gly Ile Trp Ile Pro Asp Gly Glu Asn Val Lys Ile Pro Val Ala
740 745 750

Ile Lys Val Leu Arg Glu Asn Thr Ser Pro Lys Ala Asn Lys Glu Ile
755 760 765

FIG. 20. (CONTINUED)

46/47

Leu Asp Glu Ala Tyr Val Met Ala Gly Val Gly Ser Pro Tyr Val Ser
770 775 780

Arg Leu Leu Gly Ile Cys Leu Thr Ser Thr Val Gln Leu Val Thr Gln
785 790 795 800

Leu Met Pro Tyr Gly Cys Leu Leu Asp His Val Arg Glu His Arg Gly
805 810 815

Arg Leu Gly Ser Gln Asp Leu Leu Asn Trp Cys Val Gln Ile Ala Lys
820 825 830

Gly Met Ser Tyr Leu Glu Glu Val Arg Leu Val His Arg Asp Leu Ala
835 840 845

Ala Arg Asn Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr Asp
850 855 860

Phe Gly Leu Ala Arg Leu Leu Asp Ile Asp Glu Thr Glu Tyr His Ala
865 870 875 880

Asp Gly Gly Lys Val Pro Ile Lys Trp Met Ala Leu Glu Ser Ile Leu
885 890 895

Arg Arg Arg Phe Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr
900 905 910

Val Trp Glu Leu Met Thr Phe Gly Ala Lys Pro Tyr Asp Gly Ile Pro
915 920 925

Ala Arg Glu Ile Pro Asp Leu Leu Glu Lys Gly Glu Arg Leu Pro Gln
930 935 940

Pro Pro Ile Cys Thr Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp
945 950 955 960

Met Ile Asp Ser Glu Cys Arg Pro Arg Phe Arg Glu Leu Val Ser Glu
965 970 975

Phe Ser Arg Met Ala Arg Asp Pro Gln Arg Phe Val Val Ile Gln Asn
980 985 990

Glu Asp Leu Gly Pro Ser Ser Pro Met Asp Ser Thr Phe Tyr Arg Ser
995 1000 1005

Leu Leu Glu Asp Asp Asp Met Gly Glu Leu Val Asp Ala Glu Glu Tyr
1010 1015 1020

FIG. 20. (CONTINUED)

47/47

Leu Val Pro Gln Gln Gly Phe Phe Ser Pro Asp Pro Ala Leu Gly Thr
 1025 1030 1035 1040

Gly Ser Thr Ala His Arg Arg His Arg Ser Ser Ser Ala Arg Ser Gly
 1045 1050 1055

Gly Gly Glu Leu Thr Leu Gly Leu Glu Pro Ser Glu Glu Pro Pro
 1060 1065 1070

Arg Ser Pro Leu Ala Pro Ser Glu Gly Ala Gly Ser Asp Val Phe Asp
 1075 1080 1085

Gly Asp Leu Ala Val Gly Val Thr Lys Gly Leu Gln Ser Leu Ser Pro
 1090 1095 1100

His Asp Leu Ser Pro Leu Gln Arg Tyr Ser Glu Asp Pro Thr Leu Pro
 1105 1110 1115 1120

Leu Pro Pro Glu Thr Asp Gly Tyr Val Ala Pro Leu Ala Cys Ser Pro
 1125 1130 1135

Gln Pro Glu Tyr Val Asn Gln Pro Glu Val Arg Pro Gln Ser Pro Leu
 1140 1145 1150

Thr Pro Glu Gly Pro Pro Pro Pro Ile Arg Pro Ala Gly Ala Thr Leu
 1155 1160 1165

Glu Arg Pro Lys Thr Leu Ser Pro Gly Lys Asn Gly Val Val Lys Asp
 1170 1175 1180

Val Phe Ala Phe Gly Gly Ala Val Glu Asn Pro Glu Tyr Leu Ala Pro
 1185 1190 1195 1200

Arg Ala Gly Thr Ala Ser Gln Pro His Pro Ser Pro Ala Phe Ser Pro
 1205 1210 1215

Ala Phe Asp Asn Leu Tyr Tyr Trp Asp Gln Asn Ser Ser Glu Gln Gly
 1220 1225 1230

Pro Pro Pro Ser Thr Phe Glu Gly Thr Pro Thr Ala Glu Asn Pro Glu
 1235 1240 1245

Tyr Leu Gly Leu Asp Val Pro Val
 1250 1255

FIG. 20. (CONTINUED)